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Asymmetric reduction of perfluoroalkyl ketones with chiral lithium alkoxides

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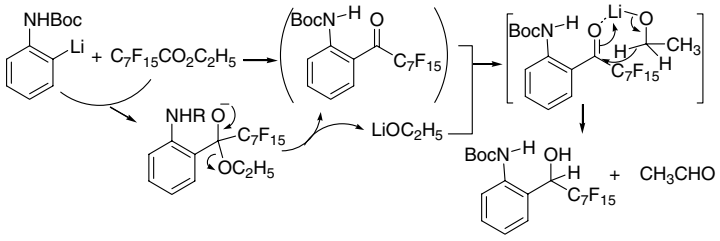
Abstract—Reduction of perfluoroalkyl ketones with chiral lithium alkoxides gave chiral α-perfluoroalkyl alcohols in high enantiomeric excesses. Interestingly, reaction of 2,2,2-trifluoroacetophenone (**1**) with lithium (*S*)-1-phenylethoxide (**2**) gave (*S*)-2,2,2-trifluoro-1-phenylethanol (**3**), while the same reaction of perfluorooctan-1-one (**7**) with **2** gave (*R*)-1*H*-1-phenylperfluorooctanol (**8**). Based on the speculation of mechanism, the order of steric effects on this reaction is estimated as C_7F_{15} > substituted phenyl > CF_3.

Nowadays, asymmetric synthesis is one of the most important topics in organic chemistry. For this purpose, we have synthesized (*R*a)-2,2′-bis{(*R*)-1*H*-1-hydroxyperfluoroalkyl}biphenyls, axially dissymmetric ligands with two chiral centers.[1] These ligands showed high asymmetric induction for the reaction of benzaldehyde with diethylzinc in the presence of Ti(O*i*Pr)$_4$. This high asymmetric induction owes to high stability and high steric constraint of 1*H*-1-hydroxyperfluoroalkyl group. Thus, we designed another ligand with this group and *ortho*-nitrogen functionality. For this purpose, we planned to synthesize *tert*-butyl *N*-[(perfluorooctanoyl)phenyl]carbamate by the reaction of the corresponding aryllithium with ethyl perfluorooctanoate.[2] Interestingly, we obtained not the objective ketone but its reduction product, as shown in Scheme 1. We examined the mechanism of this reduction, and found that lithium ethoxide played an important role in this reduction.[2] This reaction proceeds with various aromatic perfluoroalkyl ketones in good to excellent yields, especially when lithium isopropoxide is used.

Based on these results, we expected that asymmetric reduction could be induced if a chiral lithium alkoxide was used. In this letter, we would like to report the asymmetric reduction of perfluoroalkyl ketones with chiral lithium alkoxides carried out on the above expectation.



Scheme 1.

Keywords: Asymmetric reduction; Chiral transfer; Perfluoroalkyl ketone; Lithium alkoxide; α-(Perfluoroalkyl)carbinol; 1-Phenylethanol; Trifluoroacetophenone; Steric effect.
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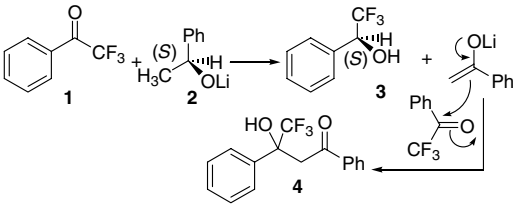
First, we chose lithium menthoxide as chiral lithium alkoxide for the reduction of 2,2,2-trifluoroacetophenone (**1**), since Nasipuri and his co-worker had reported that dichloroaluminum menthoxide showed the highest asymmetric induction of the alkoxide examined on the reduction of **1**.[3] However, lithium menthoxide gave a very low yield of the reduction product at room temperature, while raising the temperature to 70 °C improved the chemical yield but led to decrease of ee. We thought that the presence of α-phenyl group would lower the activation energy required for the reaction, allow the reduction proceed at lower temperature, and hence improve the enantioselectivity of the reaction. So, we examined lithium (*S*)-1-phenylethoxide (**2**) as a reducing agent. The reaction of **1** with **2** at room temperature produced a reduced alcohol (**3**) in moderate yield (53%) and ee (55%). Lowering the temperature from room temperature to 0 °C had a good effect in improvement of the ee up to 80% but slight improvement on the yield (63%), due to the formation of aldol adduct (**4**) as a side product that was formed by the reaction of **1** and acetophenone enolate. The absolute configuration of the resulting alcohol (**3**) was determined to be (*S*) based on the direction of optical rotation (Scheme 2).[4]

This result encouraged us to investigate this chiral reduction of other perfluoroalkyl ketones, since we had reported that the byproduct from aldol reaction was not obtained on the reduction of a larger perfluoroalkyl ketones with lithium alkoxide. The results with other perfluoroalkyl ketones are shown in Table 1.[5]

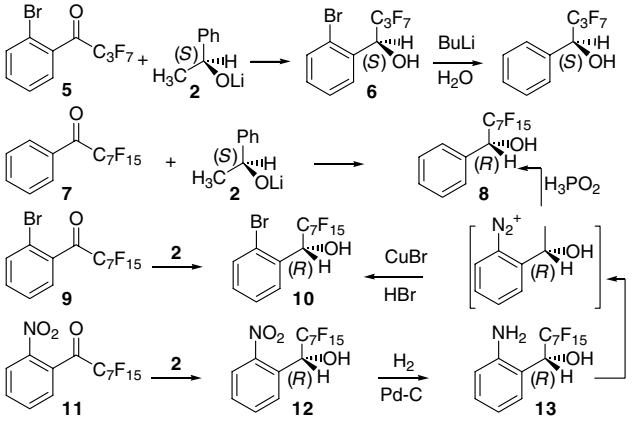
A little larger perfluoropropyl ketone, 1-(2-bromophenyl)perfluorobutan-1-one (**5**) gave the reduction product of the same configuration as that of **3** in 78% yield with 87% ee without formation of an aldol product, while more bulky perfluoroheptyl ketones, 1-phenylperfluorooctan-1-one (**7**) and its *ortho* bromo (**9**) and *ortho* nitro (**11**) derivatives, gave better chemical yields up to 80% of the reduction products (**8**, **10**, and **12**) of (*R*)-configuration with high ee's. Interestingly, absolute configurations of latter three products are opposite to the smaller analogs.

The determination of the absolute configuration of these products seemed to be rather difficult, since Mosher esters are not productive in our case of perfluoroalkyl alcohols. We determined stereochemistry of these isomers by chemical transformation.[7] Thus, **6** was debrominated by lithiation followed by treatment with water to the known (*S*)-1*H*-1-phenylperfluoro-1-butanol.[6] The alcohol (**10**) from the *ortho* bromo compound (**9**) was found to be (*R*) by comparing the retention time on a chiral GC with that of authentic sample.[1b] The nitro alcohol (**12**) from **11** was hydrogenated in the presence of Pd-C to the *ortho* amino compound (**13**), which was converted to a diazonium salt. The diazonium salt was heated with HBr–CuBr to give **10** or heated with H_3PO_2 to yield the unsubstituted phenyl derivative (**8**). So we could determine the absolute configurations of **8**, **10**, and **12** to be (*R*), as shown in Scheme 3.

The interesting point of the above results is that the reduction of **1** and **5** with (*S*)-**2** gave (*S*)-**3** and **6**, respectively, while that of **7**, **9**, or **11** afforded (*R*)-**8**, **10**, or **12**.



Scheme 2.

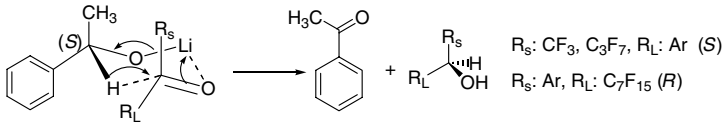


Scheme 3.

Table 1. Reduction of perfluoroalkyl ketones with lithium (*S*)-1-phenylethoxide

Ketone	Temp (°C)	Yield[a] (%)	ee[b] (%)	Abs config.
2,2,2-Trifluoroacetophenone (**1**)	rt	53	55	(*S*)-**3**[c]
2,2,2-Trifluoroacetophenone (**1**)	0	61	80	(*S*)-**3**
1-(2-Bromophenyl)perfluorobutan-1-one (**5**)	0	78	87	(*S*)-**6**[d]
1-Phenylperfluorooctan-1-one (**7**)	0	80	82	(*R*)-**8**
1-(2-Bromophenyl)perfluorooctan-1-one (**9**)	0	77	84	(*R*)-**10**[e]
1-(2-Nitrophenyl)perfluorooctan-1-one (**11**)	0	68	91	(*R*)-**12**

[a] Isolated yield.
[b] Determined by chiral GC.
[c] Determined by the sign of optical rotation.[4]
[d] (*S*)-**6** was debrominated by treatment with BuLi followed by treatment with 2 M HCl, and the sign of optical rotation was compared with the value reported.[6]
[e] Determined by comparing the chiral GC retention time to that of a predetermined authentic sample prepared by our group.[1b]



Scheme 4.

We have reported that the CBS reduction of perfluoroalkyl ketones gave a similar result and rationalized this inversion of optical rotation as the steric effects of perfluoroalkyl groups and phenyl group; $C_7F_{15} \gg Ph \geqslant C_3F_7 \gg CF_3$.[1] Surprisingly, the CBS reduction of **11** gave only 10% ee. This suggests that introduction of a nitro group to *ortho* position of a phenyl group decreases the steric difference between C_7F_{15} and Ar group and that our reduction using lithium alkoxide still differentiates this small difference. Further, the CBS reduction of **7** gave **8** in 60% ee,[1b] while this reduction of **7** gave **8** of much higher ee. This also shows that the selectivity of the reduction of this report is much higher than that of CBS reduction.

The absolute configurations of **3**, **6**, **8**, **10**, and **12** are reasonably explained by a chair-like six-membered transition state, where the larger substituents occupy the equatorial position and the smaller one the axial position in the transition state. We assume that the order of steric effects is $C_7F_{15} > Ar \geqslant C_3F_7 > CF_3$, where Ar represents (un)substituted phenyl groups. If this assumption is correct, **1** and **5** would give (*S*)-products preferentially, and **7**, **9**, or **11** would give the corresponding (*R*)-products. These are consistent with the observed results, which supports our assumption (Scheme 4).

In conclusion, treatment of perfluoroalkyl aromatic ketones can be reduced to chiral α-perfluoroalkyl alcohols with chiral lithium 1-phenylethoxide in high enantiomeric excesses. This reduction is especially useful for reduction of aromatic perfluoroalkyl ketones with a large perfluoroalkyl group, and (*S*)-1-phenylethoxide gives (*R*)-perfluoroalkyl alcohols in good yields and high ee, while trifluoromethyl ketone gives (*S*)-alcohol. This reduction is useful for reduction of perfluoroalkyl ketones, of which the CBS reduction does not give good results. This reaction is a modification of Meerwein–Pondorf–Verley's reduction. This reaction is an equilibrium reaction and cannot be applied for chiral reduction of hydrocarbon analogs, but a perfluoroalkyl group stabilizes adjacent sp^3 carbon. Thus, this method is quite useful for synthesis of chiral perfluoroalkyl carbinols.

References and notes

1. (a) Omote, M.; Kominato, A.; Sugawara, M.; Sato, K.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **1999**, *40*, 5583–5585; (b) Omote, M.; Nishimura, Y.; Sato, K.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **2005**, *46*, 319–322; (c) Omote, M.; Nishimura, Y.; Sato, K.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2005**, *126*, 407–409.
2. Sokeirik, Y. S.; Sato, K.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2006**, *127*, 150–152.
3. Nasipuri, D.; Bhattacharya, P. K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 576–578.
4. Compound **3** is commercially available..
5. *General procedure for the reduction*. To a solution of (*S*)-1-phenylethanol (0.46 mmol, 56 mg, 0.055 mL) in dry toluene (3.0 mL) was added *n*-BuLi (1.58 M in hexane, 0.29 mL, 0.46 mmol) at 0 °C. To the resulting mixture was added slowly the corresponding perfluoroalkyl ketone (0.38 mmol). The mixture was stirred for additional 16 h, and then quenched with 2 N HCl. After separation of the two phases, the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, and evaporated under vacuum. The residue was purified as shown for each case.

(S)-2,2,2-Trifluoro-1-phenylethanol (**3**). The residue was separated by column chromatography (SiO_2, 5% Et_2O in hexane) to give **3** (40.1 mg, 61%), which was identified by comparison of the spectral data of the commercially available authentic sample.[4] ^1H NMR ($CDCl_3$) δ: 7.38–7.71 (5H, m), 4.98–5.06 (1H, m), 2.62 (1H, s, disappeared with D_2O). ^{19}F NMR ($CDCl_3$) δ: (from $C_6H_5CF_3$): −15.25 (3F, d, $J = 6.2$ Hz). IR (neat) cm^{-1}: 3450. $[\alpha]_D^{22}$ +33.02 (*c* 0.92, $CHCl_3$). 4,4,4-Trifluoro-3-hydroxy-1,3-diphenyl-butan-1-one (**4**) was eluated with 10% Et_2O in hexane as a colorless oil (28.0 mg, 25%). ^1H NMR ($CDCl_3$) δ: 7.94–7.91 (2H, m), 7.59–7.55 (3H, m), 7.50–7.47 (2H, m), 7.37–7.31 (3H, m), 4.04 (1H, d, $J = 17$ Hz), 3.64 (1H, d, $J = 17$ Hz). ^{19}F NMR ($CDCl_3$) δ: −17.59 (3F, s). MS *m/z* 294 (M^+). HRMS calcd for $C_{16}H_{13}F_3O_2$: 294.087 (M^+), found: 294.087. IR (neat) cm^{-1}: 3472, 1672.

(S)-1H-1-(2-Bromophenyl)perfluorobutan-1-ol (**6**). The residue was treated with $NaBH_4$ (70 mg, 1.84 mmol) in MeOH (3 mL) for 18 h at room temperature to reduce the side product, acetophenone, and to facilitate its removal. The mixture was quenched with water and extracted with Et_2O (3 × 5 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by column chromatography (SiO_2, 5% Et_2O in hexane) to give **6** (127 mg, 78%) as a colorless oil, $[\alpha]_D^{22.2}$ +22.39 (*c* 1.68, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.70–7.66 (1H, m), 7.61–7.58 (1H, m), 7.43–7.37 (1H, m), 7.29–7.23 (1H, m), 5.86 (1H, m), 3.16 (1H, br s, disappeared with D_2O). ^{19}F NMR ($CDCl_3$) δ: −18.31 to −18.99 (3F, m), −53.25 (1F, m), −63.22 to −64.04 (3F, m). MS *m/z* 354 (M^+). HRMS calcd for $C_{10}H_6{}^{79}BrF_7O$: 353.949 (M^+), found: 353.949, HRMS calcd for $C_{10}H_6{}^{81}BrF_7O$: 355.947 (M^+), found: 355.946. IR (neat) cm^{-1}: 3520.

(R)-1H-1-Phenylperfluorooctan-1-ol (**8**). The residue was purified by column chromatography (SiO_2, 5% Et_2O in hexane) to give **8** (144 mg, 80%) as white crystals. Mp 63–64 °C. ^1H NMR ($CDCl_3$) δ: 7.49–7.36 (5H, m), 5.23–5.18 (1H, m), 2.53 (1H, s, disappeared with D_2O). ^{19}F NMR ($CDCl_3$) δ: −18.36 (3F, m), −53.50 (1F, m), −57.10 to −60.35 (8F, m), −62.50 (2F, m), −63.25 (1F, m). MS *m/z* 476 (M^+). HRMS calcd for $C_{14}H_7F_{15}O$: 476.025 (M^+), found: 476.025. IR (KBr) cm^{-1}: 3480. $[\alpha]_D^{21.5}$ +15.67 (*c* 0.95, $CHCl_3$).

(R)-1H-1-(2-Bromophenyl)perfluorooctan-1-ol (**10**). The residue was purified by column chromatography (SiO_2,

2% Et_2O in hexane) to produce **10** (162 mg, 77%) as a white solid. This was identified with the authentic sample by the following spectral data.[1b] Mp 42 °C (lit. 43.5 °C). ^1H NMR ($CDCl_3$) δ: 7.70–7.67 (1H, m), 7.61–7.59 (1H, m), 7.43–7.39 (1H, m), 7.29–7.26 (1H, m), 5.90 (1H, m), 2.78 (1H, br s disappeared with D_2O). ^{19}F NMR ($CDCl_3$) δ: −17.59 to −18.19 (3F, m), −51.50 (1F, m), −58.17 to −59.84 (8F, m), −62.78 to −63.35 (2F, m), −65.32 (1F, m). $[\alpha]_D^{22.2}$ +13.81 (*c* 0.115, $CHCl_3$).

(R)-1H-1-(2-Nitrophenyl)perfluorooctan-1-ol (**12**). The residue was first dried at 60 °C at 1 mmHg to remove the volatile material and purified by column chromatography (SiO_2, 5% Et_2O in hexane) to give **10** (134 mg, 68%) as a yellow oil. ^1H NMR ($CDCl_3$) δ: 8.03–7.99 (2H, m), 7.74–7.71 (1H, m), 7.58–7.54 (1H, m), 6.50 (1H, m), 3.92 (1H, br s, disappeared with D_2O). ^{19}F NMR ($CDCl_3$) δ: −17.50 to −18.33 (3F, m), −52.50 (1F, m), −58.17 to−60.82 (8F, m), −62.78 to −63.35 (2F, m), −65.32 (1F, m). MS *m/z* 521 (M^+) HRMS calcd for $C_{14}H_6F_{15}NO_3$: 521.011 (M^+), found: 521.011. IR (neat) cm^{-1}: 3528. $[\alpha]_D^{21.7}$ +167.16 (*c* 0.107, $CHCl_3$).

6. The reported $[\alpha]_D$ for (*S*)-isomer is +23.2. Ramachandran, V.; Teodorvic, A.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725–1738.
7. Experiments for synthesis of starting material and determination of the absolute configurations are as follows.

1H-1-Phenylperfluorobutan-1-ol. A solution of **6** (50 mg) in THF (3 mL) was treated with *n*-BuLi (0.17 mL of 2.55 M solution in hexane, 0.42 mmol) at −78 °C, The reaction mixture was stirred for 2 h at the same temperature, then quenched with 2 N HCl and extracted with Et_2O. The collected organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (SiO_2, 10% Et_2O in hexane) to give 1*H*-1-phenylperfluorobutan-1-ol (27 mg, 70%) as a colorless oil $[\alpha]_D^{22}$ +22.787[6] (*c* 1.06, EtOH). Ee = 78% (checked by chiral GC). ^1H NMR ($CDCl_3$) δ: 7.46–7.42 (5H, m), 5.17 (1H, m), 2.61 (1H, br s, disappeared with D_2O). MS *m/z* 354 (M^+).

1-(2-Nitrophenyl)perfluorooctan-1-one (**11**). To a solution of 2-bromonitrobenzene (5.00 g, 24.8 mmol) in THF (120 mL) at −100 °C was added *n*-BuLi in hexane (1.58 M, 17.2 mL, 27.2 mmol) over a period of 45 min. The resulting mixture was stirred for an additional 1 h at the same temperature. To this solution was added methyl perfluorooctanoate (6.55 mL, 27.2 mmol) over a period of 20 min, and the resulting mixture was kept at this temperature under stirring for additional 6 h. The mixture is quenched with 2 M HCl (50 mL), and the whole mixture was extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$, and evaporated under vacuum to give an oily black mass, which is purified by column chromatography (SiO_2, 2% Et_2O in hexane). The resulting solid was recrystallized from hexane to give 6.50 g (51%) of pale yellow crystals. Mp 53.0–54.0 °C. ^1H NMR ($CDCl_3$) δ: 8.34–8.31 (1H, m), 7.91–7.87 (1H, m), 7.83–7.79 (1H, m), 7.50–7.48 (1H, m). ^{19}F NMR ($CDCl_3$) δ: −17.56 (3F, m), −53.50 to −55.30 (2F, m), −57.50 to −61.50 (8F, m), 62.50–64.00 (2F, m). MS *m/z* 520 $(M+1)^+$. HRMS calcd for $C_{14}H_5F_{15}NO_3$: 520.003 $(M+1)^+$, found: 520.003. IR (KBr) cm^{-1}: 1748.

Diazotization of **13**: *1H-1-(2-bromophenyl)perfluorooctan-1-ol* (**10**).

1*H*-1-(2-Aminophenyl)perfluorooctan-1-ol (**13**, 40 mg) was treated with 48% HBr (1 mL) and cooled in ice bath to 0 °C. To this suspension was added a solution of sodium nitrite (20 mg) in H_2O (0.5 mL) so slowly as not to allow the temperature exceed 0 °C. After complete addition, the mixture was left standing for 15 min and then added at once to a hot solution of CuBr (40 mg) in 48% HBr (1 mL). The mixture was boiled for additional 1 h. The mixture was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated under vacuum. The residue was passed through a flash column chromatography (SiO_2, 5% Et_2O in hexane) to remove coloring material and analyzed without further purification with GC with the authentic sample **10** (a capillary column: TC-5 (GL Sciences Inc, 0.25 mm × 15 m), temp 80–200 °C. Retention time: Authentic sample (CBS reduction): 6.85 min. Diazonium produced sample: 6.87 min. Chiral column: GAMMA DEX^{TM} (Spelco, 0.25 mm × 30 m). Temp 150 °C, Authentic sample (CBS reduction): major peak; 12.98 min, minor peak; 13.41. Sample produced in this experiment: major peak; 12.97 min, minor peak; 13.40).

1H-1-Phenylperfluorooctan-1-ol (**8**). 1*H*-1-(2-Aminophenyl)-perfluorooctan-1-ol (40 mg, 13) was dissolved in 50% hypophosphorous acid (2 mL) and cooled in an ice bath to 0 °C, To this suspension was added $NaNO_2$ (solid, 20 mg) slowly, and then the mixture was left standing for 15 min at the same temperature, then the mixture was boiled for 1 h. After cooled to room temperature, the mixture was extracted with Et_2O. The organic phase was dried over $MgSO_4$, and evaporated under vacuum. The residue was passed through a flash column chromatography (SiO_2, 10% Et_2O in hexane) to remove coloring material and analyzed with GC without further purification to compare the retention time with compound **8** (nonchiral column, temp 80–200 °C/min). Retention time: sample from chiral reduction with Li alkoxide; 4.296 min. Sample from diazotization: 4.303. Chiral column temp 150 °C. The former sample: minor peak; 6.963 min, major peak; 7.240 min. The latter sample: minor peak; 6.940, major peak; 7.246 minor peak; 7.246 min.